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(54) Title: USE OF FORMS OF HYALURONIC ACID (HA) FOR THE TREATMENT OF CANCER

(57) Abstract

A method is provided for the treatment of cancer comprising administering orally or systemically (intravenously preferably) of an effective dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof as the only therapeutic agent, in a diluent, in such amounts and over such period of time to permit the successful treatment of cancer.

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TITLE OF INVENTION

USE OF FORMS OF HYALURONIC ACID (HA) FOR THE TREATMENT OF CANCER

FIELD OF INVENTION

This invention relates to the use of forms of hyaluronic acid for example, hyaluronic acid and pharmaceutically acceptable salts thereof such as sodium hyaluronate for the treatment of cancer.

BACKGROUND OF THE INVENTION

Forms of hyaluronic acid have been disclosed for different purposes. In this regard, see, for example, *United States Patent 4,141,973 and European Patent 0 197718B1.*

Hyaluronic acid has been previously used for the transportation/delivery of medicines and therapeutic agents to sites in need of treatment in the body for the treatment of cancer *(see International Publication WO 91/04058)* which teaches as follows:

(i) *at page 17, line 3 to page 18, line 16*:

"Applicants have now discovered that combinations and formulations (for example an injectable formulation) can be provided for administration to a mammal for the treatment of a disease or condition, which combinations or formulations employ or incorporate as the case may be a therapeutically effective non-toxic amount of a medicinal and/or therapeutic agent to treat the disease or condition (for example a free radical scavenger (for example ascorbic acid (Vitamin C)), Vitamin C (for the treatment of mononucleosis), an anti-cancer agent, chemotherapeutic agent, anti-viral agents for example a nonionic surfactant, e.g. nonoxynol-9 [nonylphenoxy polyethoxy ethanol] found in Delfen™ contraceptive cream, and anionic surfactants (e.g. cetyl pyridinium chloride) and cationic surfactants (e.g. benzalkonium chloride), non-steroidal anti-inflammatory drugs (NSAID) for example indomethacin, naproxen and (+/-) tromethamine salt of ketorolac (sold under the trademark Toradol™) and steroidal anti-inflammatory drugs, anti-fungal agent, detoxifying agents (for example for administration rectally in an enema), analgesic, bronchodilator, anti-bacterial agent, antibiotics, drugs for the

treatment of vascular ischemia (for example diabetes and Berger's disease), anti-body monoclonal agent, minoxidil for topical application for hair growth, diuretics (for example furosemide (sold under the trademark Lasix™)), immunosuppressants (for example cyclosporins), lymphokynes (such as interleukin - 2 and the like), alpha-and-ß-interferon and the like) administered with, or carried in, an amount of hyaluronic acid and/or salts thereof (for example the sodium salt) and/or homologues, analogues, derivatives, complexes, esters, fragments, and/or sub units of hyaluronic acid (preferably hyaluronic acid and salts thereof) sufficient to facilitate the agent's penetration through the tissue (including scar tissue), at the site to be treated through the cell membranes into the individual cells to be treated. When such combinations and formulations are administered to patients suffering from the disease or condition, the disease or condition is unexpectedly improved.

The formulation can be administered among other methods, intravenously, intra arterially, intraperitoneally, intrapleurally, transdermally, on the skin (topically), rectally, orally or by direct injection (for example into a tumor, into an abscess or similar disease focus) or put on a patch to be secured to the skin of the patient. The hyaluronic acid and/or salts thereof and the agent can be administered separately but are administered in sufficient amounts and in an immediate time sequence or interval (preferably concurrently and more preferably simultaneously), preferably at the identical site (e.g. one given intravenously and the other "piggy backed"), to treat the disease or condition."

(ii) *at page 24, lines 13-33*:

"The combination of hyaluronic acid and salts thereof and other forms with different chemicals and drugs (Vitamin C, anti-cancer drugs, etc.) alters their distribution and performance in the human body and produces an unusual targeting for underperffused tissue and/or pathological tissue. In this regard, the use of ascorbic acid (Vitamin C) as a free radical scavenger (50 gm daily - 1000 times the daily dose

in therapeutic purposes as a Vitamin) administered intravenously with 300 - 500 mg of hyaluronic acid (sodium hyaluronate) immediately relieves bone pain and muscle pain and reduces inflammation in cancer patients. The hyaluronic acid enhances the anti-neoplastic activity and effect of the ascorbic acid. It is thought that this enhanced activity eliminates the free radicals by acting as a free radical scavenger. In any event the patients feel better. This is also demonstrated with furosemide and hyaluronic acid where the activity of furosemide is enhanced only minimally when administered with hyaluronic acid to a "normal" subject but the activity is enhanced significantly when administered to a patient whose kidney is underperfused or malfunctioning due to insufficient intra-vascular volume."

(iii) *at page 25, line 18 to page 26, line 14*:

"Thus and according to another aspect of the invention when an NSAID for example indomethacin (dissolved in n-methyl glucamine) or other NSAID is administered with greater than 200mg hyaluronic acid for 1 - 2 mg/kg body weight of the NSAID (in one instance indomethacin and NMG), no major toxic side effects occur such as gastro-intestinal distress, neurological abnormalities, depression, etc., even at elevated amounts of indomethacin (if necessary). If the amount of hyaluronic acid is decreased below that amount, the usual side effects may begin to reoccur. In addition, the responses that have been observed are superior when the NSAID (for example Indocid™) is combined with hyaluronic acid demonstrating clearly that the combination is now "targeting" to the pathological tissue even when administered by the systemic intravenous route. Thus, it has been observed that patients with neoplastic diseases when receiving in addition to other chemicals (for example ascorbic acid [Vitamin C], phloretin and anti-cancer drugs), 50 - 200 mg NSAID - hyaluronic acid (sodium hyaluronate) (for example indomethacin and hyaluronic acid) experience dramatic relief of pain immediately. This is followed within a short period of time by a resolution and resorbtion of neoplastic lesions with an improvement of

pulmonary, and liver function if there is tumor present in these organs. Thus the dead tumor material and the debris and tumor toxins appear to be better eliminated by the body through the action of the macrophages whose activity is enhanced by the addition of the NSAID (or a steroidal anti-inflammatory drug) administered with hyaluronic acid (or salt or other form thereof). Thus Applicants believe that the addition of the NSAID for example with hyaluronic acid (sodium hyaluronate) deblocks the macrophages by preventing enzymatic production of prostaglandin synthetase which blocks macrophage functioning. Thus the hyaluronic acid (and salt and other forms) not only enhance the activity of the NSAID but also reduce any side effects and toxicity that is associated with the use of the prostaglandin synthesis inhibitors.

Examples of agents suitable for use as chemotherapeutic agents are novantrone (Mitoxantrone), Methotrexate, 5-FU (5-Fluorouracil), carboplatinum, methyl CCNU administered orally and Mitomycin C."

(iv) *at page 26, lines 32 to 37:*

"The hyaluronic acid and salts thereof may be utilized at varying doses - 10 to 1000 mg/70 kg person with the optimal doses tending to range between 50 and 350 mg/70 kg individual. As there is no toxicity, the hyaluronic acid can obviously be administered in a dose excess (for example 3000 mg/70 kg individual) without any adverse effects."

(v) *and, at page 33, line 37 to page 35, line 30:*

"Thus Applicant has combined hyaluronic acid (and sodium hyaluronate and/or other forms) with medicinal and/or therapeutic agents for the treatment of conditions and diseases with totally unexpected results:

For Example

Condition/Disease	Chemicals & Drugs
1. Cancer, increasing activity of macrophages	free radical scavenger, superoxide dismutase, ascorbic acid(Vitamin C) anti-cancer drugs, NSAID, Chemotherapeutic Agents,

			detoxifying Agents (e.g. cholestyramine)
	1A.	Reduction of swelling in brain of	Dimethyl Sulfoxide
5		(DMSO)person suffering brain trauma	
	2.	Hair growth grow more hair when applied topically	minoxidil - combination -
	3.	Herpes, canker sore,	nonionic surfactants, e.g.,
10		shingles	nonoxynol-9 and anionic, (e.g. cetyl pyridinium chloride) and cationic (e.g. benzalkonium chloride),
15			surfactants
	4.	Renal failure, cardiac insufficiency, hypertension, edema	diuretics - furosemide
	5.	Infection, acne,	antibiotics, antibacterials,
20		mononucleosis	antimicrobials, etc., ascorbic acid and hyaluronic acid
	6.	Transplants	cyclosporins
	7.	Inflammation, elimination of	non-steroidal anti-inflamma-
25		tumor break down material	tories, NSAID e.g. (toxins and debris), diclofenac,
		decreasing side effects,	indomethacin, piroxicam,
		relief of pain (e.g.	ibuprofen, tromethamine salt
30		back pain)	of Ketorolac, naproxen,
	8.	Detoxification	enema, detoxifying agent, peritoneal dialysis
	9.	Bronchodilation	bronchodilators, e.g. beclo- methasone diproprionate
35			(sodium cromoglycate although not specifically a broncho- dialator), theophylline
	10.	Vascular ischemia	treat limbs in respect of

		diabetes, Berger's disease, etc.
	with	suitable medicine e.g. Trental
11.	HIV (AIDS)	DMSO, Vitamin C, NSAID (e.g. indomethacin, naproxen, ketorolac tromethamine), interferon, Vibramycin™, (doxycline), tetracycline
12.	Diabetes	insulin
13.	Post-menopause	estrogens replacement
14.	Prevention of topical	antimetabolites (e.g. infection sulfonamides)
15.	Reduction of swelling	DMSO
16.	Hypertension, cardiac	Calcium channel blockers e.g. insufficiency- Nifedipine ß-
	Blockers	e.g. atenolol, propranolol
17.	Prostaglandin Synthesis inhibition	acetylsalicylic acid
18.	Enhance oxygenation of tissue by perfusion fluid bathing the tissue (for transplantation purposes"	perfusate

Hyaluronic acid has not been used for the treatment of cancer by itself. In this regard, Applicant is aware of International Publication No. WO 94/20115 (by Miles, Inc.) which purports to teach preparations containing hyaluronic acid for the treatment of cancer. The hyaluronic acid preparations for the treatment of cancer include lipoteichoic acid. This is clear from the examples of treatment taught.

In ***Example 1***, a nine year old terrier dog was treated with dosages of 1% hyaluronic acid and 10µg/ml of lipoteichoic acid administered regularly until four months after treatment when the dog began suffering seizures from what the veterinarian diagnosed as melanoma metastasis to the brain.

> "At this point, it was decided to increase hyaluronic acid treatment rate. One mL intramuscular doses were injected at weekly intervals. This was continued for two years." *(page 5, lines 22-25)*

By this time, the dog would have been 11 and the disease may have been successfully treated. In any event, between the dog's eleventh and thirteenth years,

> "no lipoteichoic acid was added to the hyaluronic acid and the rate of injection has been reduced to 1.0 mL IM/month. The dog is now 13 years old. She has no signs of melanoma and functions well." *(page 5, lines 26-29)*

There is no evidence that the hyaluronic acid by itself cleared the cancer.

In the only other example, ***Example*** 2, a four year old boxer dog was treated.

> "The inventor of this patent gave the individual a preparation containing 1% hyaluronic acid and 10 µg/ml of lipoteichoic acid to try. The owner injected it as often as necessary (1.0 mL intramuscularly up to 3 times per day)." *(page 6, lines 12-16)*
>
> "By three months, the preparation was required only on a weekly basis." *(page 6, lines 21-22)*

The lipoteichoic acid was discontinued "at this point in time" *(page 6, line 23)*. The nodules have disappeared. However, once again, there is no evidence that hyaluronic acid by itself cleared the cancer.

The Turley article published *Cell, Vol. 62, 1-20, July 14, 1995* entitled **"Over expression of the Hyaluronan Receptor (RHAMM) is Transforming and is also Required for H-ras Transformation"** proposes that hyaluronan may be used in certain neoplastic transformation situations to alter the function of abnormal cells.

Where cytotoxic agents are used to treat cancer, the use of cytotoxic agents and other agents subjects the patient to the effects of the cytotoxic agents in the body. Even by using an NSAID agent with in excess of 200 mg./70 kg. person of hyaluronic acid (taught in WO 91/04058) causing the side effects normally accompanying the use of the NSAID, such as gastro-intestinal distress, neurological abnormalities, depression, etc., to disappear even at elevated amounts of the NSAID, the NSAID is still present. Where a cytotoxic agent is present, even if the form of HA reduces the side effects of the cytotoxic agent's use the body is still subjected to the medicine. As cancer is a disease which weakens the body and its immune response, where possible, the additional medicines if not

needed should be deleted so as not to overly tax the patient's bodily functions.

It is therefore an object of this invention to provide improved treatments for the treatment of cancer.

It is a further object of this invention to provide such treatments which are more easily tolerable to the patient.

It is a further object of this invention to provide such treatments which have minimal side effects.

It is still a further object of this invention to provide such treatments over such time as is required to successfully treat the patients.

It is still a further object of this invention to provide suitable dosages for such treatments.

Further and other objects of the invention will be realized by those persons skilled in the art from the following summary of the invention and detailed examples illustrating the invention.

SUMMARY OF THE INVENTION

According to one aspect of the invention, a novel process for the treatment of cancer is provided comprising the oral or systemic (intravenous preferably) administration of a form of hyaluronic acid as the active agent selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof in amounts and over such period of time to permit the successful treatment of cancer - either remission or full elimination or, at least, until such time and for such duration to stop or reduce the growth of the cancer cells so that the patient's condition does not deteriorate further. The administration is of hyaluronic acid as the active agent in a suitable diluent (such as saline or sterile water) without any further active agents to treat the cancer in amounts that are usually considered, by persons skilled in the art, larger amounts of hyaluronic acid in each dosage for example, exceeding 750 mg. per 70 kg. person and preferably, exceeding 1 g. per 70 kg. person for each dosage given. Thus, the dosages consist only of a form of hyaluronic acid for example, hyaluronic acid and/or a pharmaceutically acceptable form thereof (for example, sodium hyaluronate) as the active agent without any other active, in a diluent.

Hyaluronic acid in such amounts, however, can also be, if preferable or desirable, administered with agents which detoxify the patient (*see for example, WO91/04058* which teaches such detoxification and whose teachings are incorporated herein by reference) or the use of an

NSAID for inhibiting prostaglandin synthesis if suitable or with a cytotoxic agent (chemotherapeutic agent) such as 5-FU (5-Fluorouracil). However, the invention is different from the invention described in WO91/04058 (now issued in Europe as European Patent No. 0445255) because the hyaluronic acid is the active agent which, in fact, acts upon the cancer. The use of the form of hyaluronic acid as the active agent in the treatment of cancer, especially by larger dosages, has not been recognized.

Additionally, according to another aspect of the invention, a novel method for the treatment of cancer of a patient is provided comprising administration of at least two courses of therapy, one course comprising administration of a form of hyaluronic acid as the active agent selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof as the active agent in amounts exceeding about 750 mg/70 kg person and preferably exceeding 1gm/70 kg person for each dosage given, in a suitable diluent for a period of time for the patient to be effected thereby (for example, the patient receiving such amounts over such a period of time for remission or reduction, of the cancer, and thereafter after a further period of time, administering another course of therapy (stage of therapy) comprising the administration of dosages to the patient, each dosage comprising an effective dosage amount of a cytotherapy (chemotherapy such as 5-FU (5-Fluorouracil)) for a further period of time.

The period between the one stage (course) of therapy (administration of dosages of hyaluronic acid as the only active agent in a diluent) and the second stage (course) (administration of the course of therapy of dosages, each dosage comprising an effective dosage amount of chemotherapy (for example, 5-FU (5-Fluorouracil)) can be in the order of 6-9 weeks.

This therapy has proved successful where improvement of the patient's condition by the administration of hyaluronic acid alone (as the active agent) in a diluent has slowed. With the administration of the following stage of therapy, the patient continues to improve. Therefore, a synergistic unexpected effect is the result. It would not be expected that the two stages of therapy administered at the spaced interval would be successful. Yet, such treatment has proven successful.

The course of treatment can be reversed with equal success. For example, the patient may be given dosage amounts of chemotherapy first (for example, the usual dosage amounts of chemotherapy such as 5-FU (5-

Fluorouracil)) for a specified period of time followed by the period when nothing is administered (for example 6-9 weeks) then followed by the course of therapy of the forms of hyaluronic acid in the amounts and for such period of time suitable for such treatment.

The results in either case are totally unexpected. A synergistic effect of giving the two courses of therapy (with the rest period therebetween) results in either reduction, remission, or elimination of the cancer.

Therefore, according to another aspect of the invention a novel method of treatment is provided comprising administering orally and/or systemically at least a two-stage course of cancer treatment, one of the courses comprising administering orally or systemically effective dosage amounts of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof as an active therapeutic agent in a suitable diluent over a suitable time period and, another course of therapy comprising administering orally or systemically effective dosage amounts of a chemotherapeutic agent (anti-cancer agent) over a suitable time period wherein a time period (rest period) of no administration of either course is provided between the stoppage of the administration of one of the courses of administration and the beginning of the other (for example second) course of administration.

According to another aspect of the invention, the said method comprises the course of administration comprising the form of hyaluronic acid being administered before the course comprising the chemotherapeutic agent.

According to another aspect of the invention, the said method comprises the course of administration comprising the chemotherapeutic agent being administered before the course of administration comprising the form of hyaluronic acid.

According to another aspect of the invention, the period of time between the end of the administration of one course of cancer treatment (hyaluronic acid and cytotherapy) and the commencement of another course of cancer treatment (the other of cytotherapy and hyaluronic acid) is between about 6-9 weeks.

As toxicity is not a concern, 3000 mg. or more of the form of hyaluronic acid may be even given patients in each dosage for the treatment without adverse effect for example, upon either oral or intravenous administration of the form of hyaluronic acid. By such treatment, there is an impact in the neoplastic tissue within 6 to 24 hours

after administration by either route. However, the effective dose may vary with the route of administration and with the tumor type, location, and the bulk and activity of the tumor.

As has now been discovered (*see Canadian Patent Application Serial No. 2,167,044* filed January 11, 1996 entitled **"Oral Administration of Effective Amounts of Forms of Hyaluronic Acid"**), forms of hyaluronic acid taken orally will not be destroyed by the upper gastric and duodenal enzyme systems. I have, therefore, given patients orally the forms of hyaluronic acid and the patients have been responding and have been successfully treated for example, with such forms penetrating between the lining of the cells of the gut and being absorbed into the lymphatic system. I have also established that the range of doses of the form of hyaluronic acid and the frequency of administration of dosages has a significant therapeutic impact on decreasing tumor cell growth and metastases in a patient. Various forms of hyaluronic acid can be administered with this invention for example, the following two formulations have been used:

FORMULATION 1

1% Sodium Hyaluronic Sterile Solution
Finished Product Specifications

Tests		Specifications
1.	Container Description	1 50 mL Flint Glass Vial with a 20 mm Rubber Stopper and 20 mm Aluminum Seal.
2.	Product Description	A clear, colourless, odourless, slightly viscous liquid.
3.	Fill Volume	50.0 to 52.0 mL
4.	pH (25 deg. C.)	5.0 to 7.0
5.	Specific Gravity (25 deg. C.)	0.990 to 1.010
6.	Intrinsic Viscosity	4.5 to 11.0 dL/g
7.	Molecular Weight	178,000 to 562,000 daltons
8.	Sodium Hyaluronate Assay	9.0 to 11.0 mg/mL
9.	Particulate Matter (USP 23)	No visible particles

10.	Sterility (USP 23)	Must pass test
11.	Bacterial Endotoxins (LAL) (USP 23)	NMT 0.07 EU/mg

FORMULATION 2

Sodium Hyaluronate Raw Material
Pharmaceutical Grade Specifications

Source: Fermentation
Manufacturer: Kyowa Hakko
Supplier: Kyowa Hakko

Tests		Specifications
1.	Description	White or cream odourless powder
2.	Identification (IR Spectrum)	Conforms to Ref. Std. Spectrum
3.	pH (1% solution)	5.0 to 7.0
4.	Loss on Drying	NMT 10%
5.	Residue on Ignition	15.0% to 19.0%
6.	Protein Content	NMT 0.1%
7.	Heavy Metals	NMT 20 ppm
8.	Arsenic	NMT 2 ppm
9.	Residual Solvents	
	a) Formaldehyde	NMT 100 ppm
	b) Acetone	NMT 0.1%
	c) Ethanol	NMT 2.0%
10.	Sodium Hyaluronate Assay (dried basis)	97.5 to 102.5%
11.	Intrinsic Viscosity	10.0 to 14.5 dL/g
12.	Molecular Weight	500,000 to 800,000 daltons
13.	Total Aerobic Microbial Count (USP 23)	NMT 50 microorganisms/g

14.	Escherichia coli (USP 23)	Absent
15.	Yeasts and Moulds (USP 23)	NMT 50 microorganisms/g
16.	Bacterial Endotoxins (LAL) (USP 23)	NMT 0.07 EU/mg

Another form of hyaluronic acid and/or pharmaceutically acceptable salts thereof (for example, sodium salt) also suitable for use with Applicant's invention is an amount having the following specifications/characteristics:

TESTS	SPECIFICATIONS	RESULTS
pH	5.0 to 7.0 at 25 degrees C.	6.0
Specific Gravity	0.990 to 1.010 at 25 degrees C.	1.004
Intrinsic Viscosity	4.5 to 11.0 dL/g.	7.07
Molecular Weight	178,000 to 562,000 daltons	319,378 daltons
Sodium Hyaluronate Assay and Identification	9.0 to 11.0 mg/mL. Positive	9.9 mg/ML Positive

Another such form of hyaluronic acid may comprise:

	TESTS	SPECIFICATIONS
1.	Description	White or cream odourless powder
2.	Identification (IR Spectrum)	Conforms to Ref. Std. Spectrum
3.	pH (1% solution)	5.0 to 7.0
4.	Loss on Drying	NMT 10%
5.	Residue on Ignition	15.0% to 19.0%
6.	Protein Content	NMT 0.1%
7.	Heavy Metals	NMT 20 ppm
8.	Arsenic	NMT 2 ppm
9.	Residual Solvents	
	a) Fomaldehyde	NMT 100 ppm
	b) Acetone	NMT 0.1%
	c) Ethanol	NMT 2.0%
10.	Sodium Hyaluronate Assay (dried basis)	97.0 to 102.0%
11.	Intrinsic Viscosity	10.0 to 14.5 dL/g

12.	Molecular Weight	500,000 to 800,000 daltons
13.	Total Aerobic Microbial Count (USP 23)	NMT 50 microorganisms/g
14.	Escherichia coli (USP 23)	Absent
15.	Yeasts and Moulds (USP 23)	NMT 50 microorganisms/g
16.	Bacterial Endotoxins (LAL) (USP 23)	NMT 0.07 EU/mg

Another such amount is available from Hyal Pharmaceutical Corporation and comes in a 15 ml vial of Sodium hyaluronate 20mg/ml (300mg/vial - Lot 2F3). The sodium hyaluronate amount is a 2% solution with a mean average molecular weight of about 225,000 daltons. The amount also contains water q.s. which is triple distilled and sterile in accordance with the U.S.P. for injection formulations. The vials of hyaluronic acid and/or salts thereof may be carried in a Type 1 borosilicate glass vial closed by a butyl stopper which does not react with the contents of the vial.

The amount of hyaluronic acid and/or salts thereof (for example sodium salt) may also comprise the following characteristics:

a purified, substantially pyrogen-free amount of hyaluronic acid obtained from a natural source having at least one characteristic selected from the group (and preferably all characteristics) consisting of the following:

i) a molecular weight within the range of 150,000-225,000;
ii) less than about 1.25% sulphated mucopolysaccharides on a total weight basis;
iii) less than about 0.6% protein on a total weight basis;
iv) less than about 150 ppm iron on a total weight basis;
v) less than about 15 ppm lead on a total weight basis;
vi) less than 0.0025% glucosamine;
vii) less than 0.025% glucuronic acid;
viii) less than 0.025% N-acetylglucosamine;
ix) less than 0.0025% amino acids;
x) a UV extinction coefficient at 257 nm of less than about 0.275;
xi) a UV extinction coefficient at 280 nm of less than about 0.25; and

xii) a pH within the range of 7.3-7.9. Preferably, the hyaluronic acid is mixed with sterile water and the amount of hyaluronic acid has a mean average molecular weight within the range of 150,000-225,000 daltons. More preferably, the amount of hyaluronic acid comprises at least one characteristic selected from the group (and preferably all characteristics) consisting of the following characteristics:

i) less than about 1% sulphated mucopolysaccharides on a total weight basis;
ii) less than about 0.4% protein on a total weight basis;
iii) less than about 100 ppm iron on a total weight basis;
iv) less than about 10 ppm lead on a total weight basis;
v) less than 0.00166% glucosamine;
vi) less than 0.0166% glucuronic acid;
vii) less than 0.0166% N-acetylglucosamine;
viii) less than 0.00166% amino acids;
x) a UV extinction coefficient at 257 nm of less than about 0.23;
xi) a UV extinction coefficient at 280 nm of less than 0.19; and
xii) a pH within the range of 7.5-7.7

Sodium hyaluronate produced and supplied by LifeCore™ Biomedical, Inc., having the following specifications may also be used:

Characteristics	Specification
Appearance	White to cream colored particles
Odor	No perceptible odor
Viscosity Average Molecular Weight	< 750,000 Daltons
UV/Vis Scan, 190-820nm	Matches reference scan
OD, 260nm	< 0.25 OD units
Hyaluronidase Sensitivity	Positive response
IR Scan	Matches reference
pH, 10mg/g solution	6.2 - 7.8
Water	8% maximum
Protein	< 0.3 mcg/mg NaHy
Acetate	< 10.0 mcg/mg NaHy
Heavy Metals, maximum ppm	
As Cd Cr Co Cu Fe Pb Hg Ni	

2.0	5.0	5.0	10.0	10.0	25.0	10.0	10.0	5.0
Microbial Bioburden						None observed		
Endotoxin						< 0.07EU/mg NaHy		
Biological Safety Testing						Passes Rabbit Ocular		
						Toxicity Test		

Another amount of sodium hyaluronate proposed to be used is sold under the name Hyaluronan HA-M5070 by Skymart Enterprises, Inc. having the following specifications:

Specifications' Test Results	
Lot No.	HG1004
pH	6.12
Condroitin Sulfate	not detected
Protein	0.05%
Heavy Metals	Not more than 20 ppm
Arsenic	Not more than 2 ppm
Loss on Drying	2.07%
Residue on Ignition	16.69%
Intrinsic Viscosity	12.75 dl/s (XW: 679,000)
Nitrogen	3.14%
Assay	104.1%
Microbiological Counts	80/g
E. coli	Negative
Mold and Yeast	Not more than 50/g

Other forms of hyaluronic acid and/or its salts may be chosen from other suppliers and those described in prior art documents provided they are suitable.

The following references teach hyaluronic acid, sources thereof, and processes for the manufacture and recovery thereof which may be suitable.

United States Patent 4,141,973 teaches hyaluronic acid fractions (including sodium salts) having:

"(a) an average molecular weight greater than about 750,000, preferably greater than about 1,200,000 - that is, a limiting viscosity number greater than about 1400 cm^3/g., and preferably greater than about 2000 cm^3/g.;

(b) a protein content of less than 0.5% by weight;

(c) ultraviolet light absorbance of a 1% solution of sodium hyaluronate of less than 3.0 at 257 nanometers wavelength and less than 2.0 at 280 nanometers wavelength;

(d) a kinematic viscosity of a 1% solution of sodium hyaluronate in physiological buffer greater than about 1000 centistokes, preferably greater than 10,000 centistokes;

(e) a molar optical rotation of a 0.1 - 0.2% sodium hyaluronate solution in physiological buffer of less than -11×10^3 degree - cm^2/mole (of disaccharide) measured at 220 nanometers;

(f) no significant cellular infiltration of the vitreous and anterior chamber, no flare in the aqueous humour, no haze or flare in the vitreous, and no pathological changes to the cornea, lens, iris, retina, and choroid of the owl monkey eye when one milliliter of a 1% solution of sodium hyaluronate dissolved in physiological buffer is implanted in the vitreous replacing approximately one-half the existing liquid vitreous, said HUA being

(g) sterile and pyrogen free and

(h) non-antigenic."

Canadian Letters Patent 1,205,031 (which refers to United States Patent 4,141,973 as prior art) refers to hyaluronic acid fractions having average molecular weights of from 50,000 to 100,000; 250,000 to 350,000; and 500,000 to 730,000 and discusses processes of their manufacture.

Where high molecular weight hyaluronic acid (or salts) is used, it may have to be diluted to permit administration and ensure no coagulation or blockage. It may also have to autoclaved to reduce the molecular weight for successful administration.

As there is no toxicity of the form of hyaluronic acid, the form of hyaluronic acid may be administered in doses in excess of 40 mg/kg, for example, 3000 mg/70 kg person or greater without adverse toxic effects.

Thus, according to another aspect of the invention, a novel method of treatment of patients with cancer may now consist of administering an effective amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof, such as sodium hyaluronate, all having a molecular weight of less than

750,000 daltons in a suitable diluent (sterile water or saline) for such period of time as required. For example, administration of one dosage every 4 to 5 days of an amount of over 1 g. of the form of hyaluronic acid per dosage either orally or systemically (for example intravenously) administered in a suitable saline or sterile water for intravenous and oral administration to the patient which dosage is then cut back as required as the patient responds or increased if the patient does not respond may be suitable. Thus, the treatments may provide periods where the treatments are weekly for a number of months, decreasing or increasing as required, adjusting each dosage up or down as required as to the amount of the form of hyaluronic acid (hyaluronan).

According to another aspect of the invention, the use of a form of hyaluronic acid selected from hyaluronic acid and pharmaceutically acceptable salts thereof (sodium hyaluronate) is provided for the treatment of cancer wherein the form of hyaluronic acid is the active component.

According to another aspect of the invention, the use of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof, for example, sodium hyaluronate, is provided for the manufacture of a pharmaceutical composition for the treatment of cancer wherein the form of hyaluronic acid is the active component for treating cancer and exceeds about 750 mg. per 70 kg. person and preferably, exceeds 1 g. of the form of hyaluronic acid per 70 kg. person per dosage in a pharmaceutically acceptable diluent such as sterile water or saline.

The invention will now be illustrated with reference to the following examples which should not be taken as limiting. The examples are merely illustrative of the invention ("d.o.b." means date of birth of the patient.) For identification, initials are used to identify persons. The initials themselves may not be indicative of the name of the person treated.

Example 1 - LB - 114 kgs., d.o.b. 1927 (Male)

This patient was diagnosed with cancer of the rectum. On February 1st, 1994 he underwent anterior resection of an advanced rectal cancer. In November 1994 he showed liver metastases and had a pelvic recurrence necessitating a colostomy. That operation confirmed the liver metastases.

He had brief post-operative chemotherapy which was not judged effective.

He was first assessed September 1995, and showed a major involvement of the liver at that time with compromised hepatic function. Experimental therapy was initiated on September 7th, 1995 and the patient received three consecutive days of intravenous administration of HA at 1000 mgs. (calculated as .9 mgs./kg body weight - weight - 114 kgs) followed by weekly treatment of the same dosage.. In December 1995, for three consecutive weekly doses he received oral HA (same amounts) and then subsequently has continued on HA intravenously weekly, since that time.

Three ultra sounds report disease regression. The patient's clinical status is that his tumours have regressed and then remained stable, now for a six month period of time. With the documented extent of disease that was present, the patient is now beyond the anticipated time period of survival. His liver function tests have improved. The CEA (carcino-embryonic antigen - a purported indicator of cancer) has fluctuated and increased, with subsequent decreases and now is apparently stable. (It must be emphasized that this CEA result is not a quantitative test of disease status when in contrast to the total clinical assessment.)

Example 2 - NT - 64 kgs., d.o.b. 1953 (Female)

This patient was first seen with wide spread metastatic cancer of the breast in May 1995. She had been initially diagnosed with breast cancer and treated for local disease. She subsequently developed metastases approximately 4 years from diagnosis. When first assessed at our clinic, the patient had wide spread metastases, including lung, liver, bone, local and cutaneous recurrence. Based on the laboratory measurement assessment that her platelets were low (40,000 per unit assessment), it was the opinion of three clinical consultants that she had bone marrow involvement.

A bone marrow aspiration to assess this was recommended by all consultants but the patient refused. It was the opinion of the various consultants that she could not

be subjected to high doses of chemotherapy, without a prohibitive possibility of negative outcome (death) through therapeutic intravention of this type.

She was treated with therapeutic cytotoxic chemotherapy given in HA as a vehicle on a number of occasions from the beginning of May onward.

There was some initial improvement in her breathing and some general improvement in her status from May, 1995 to October, 1995.

In October 1995, she was treated with Eprex (erythropoitien) a hormone stimulative for red blood cell production. In the meantime, she sought further consultation and it was recommended again that she have a bone marrow aspiration to assess the status of her bone marrow and to determine if it was involved with disease. She elected not to do that. On November 21st, 1995, she was started experimentally on an increasing dose of hyaluronic acid without additional medication. (The hyaluronic acid was the only active agent.) She received 750 mgs. on November 21st, and again on December 4, 6, 11, 13, 18, and 20 (in a diluent).

It should be noted that she had previously received hormone receptor altering drugs.

She received an additional hormone altering drug (Zoladex) at a standard dose, q 1 dose per month on November 23rd, 1995. (This hormone blocking medication had previously not effected her platelet level.) The patient therefore represents a response to HA with concomitant hormone altering drugs, which had previously been ineffective in her treatment.

Example 3 - R.E., d.o.b. 04/06/61 (Female)

This patient was diagnosed with metastatic gastric cancer - adenocarcinoma type November 30th, 1995. She was subsequently operated on and had a laparotomy done which showed diffuse metastatic cancer involving the stomach and other abdominal organs. This was biopsied. A gastrotomy tube was placed to decompress the stomach as it was anticipated the patient would within the near future,

develop gastric obstruction which would necessitate decompression.

She was first seen December 19th, 1995. She was in poor condition at that point in time. Abdominal assessment indicated the recent abdominal scar and one could feel diffuse tumor masses, compatible with the findings at laparotomy.

The patient had experimental therapy initiated with oral HA (hyaluronic acid) administered every five days, 1 gram total dose of hyaluronic acid (body weight = 70 kg) per day (each dosage was 1 g. of the form of hyaluronic acid).

She was reassessed January 3rd, 1996 and there was some demonstrable improvement. I then initiated therapy with HA intravenously at the same dose. This was repeated January 4th and again January 16, 17, 18. The patient was then treated with oral HA at the same dose weekly until February 13th, 14th, 1996 when she again received 1 gram of HA total dose I.V. (intravenously) as previously. She was then maintained on oral medication until March 5th when she again received 1 gram of HA I.V. and this was repeated on March 6th. At present she continued on oral medication weekly.

Repeated abdominal assessment has indicated that the previously noted tumor masses are not apparent. In addition, the previous discomfort that the patient experienced in her abdomen has disappeared completely.

The patient continues on oral and intravenous hyaluronan.

This patient represents a case of diffuse and metastatic adenocarcinoma of the stomach in the abdomen with initially a projected survival time of 1-3 months. Currently, she would appear to be in complete remission.

This patient has not received any other putative cytotoxic or cytostatic anti-cancer drugs.

Example 4 - K.L., d.o.b. 19/01/55 (Female)

This patient had a carcinoma of the breast resected in October 1992 with reconstructive surgery. There was lymph node involvement. She was treated at another centre

throughout this and was placed in a randomized study series but apparently drew a no-treatment arm and did not have any treatment. She then developed multiple liver metastases. Her estrogen and progesterone receptors were both positive suggesting a hormone sensitive tumor.

At that time, the patient initiated Tamoxifen therapy. I saw her very intermittently during this period of time; one could assume that she had a response because she survived and her liver function tests did improve.

Subsequently, reinvestigation indicated that her disease had progressed but she refused to remain on Tamoxifen continuously. When I saw her again on March 8th, 1995, there had been major progression of her disease. I then discontinued the Tamoxifen and indicated to her that we would initiate cytotoxic chemotherapy in minimal dose HA. She was treated with this March, 1995 and did improve over a period of time until August, 1995 with her CEA (carcino-embryonic antigen) blood level decreasing from a high of 111 to 17.9. She continued this treatment but very intermittently and by October 1995, the patient's disease again was progressing.

On December 6th, we initiated higher dose intravenous HA by itself utilizing 1 g. total dose of HA I.V. (body weight 51.1 kg.). The patient received this on a weekly basis until January 17th, 1996. By this time, she had improved dramatically. Her CEA which had previously again increased to 77.2, by January 17th had decreased to 17.

The patient has always determined her own therapy and the timing of any intervention and has not been treated. She was re-assessed in mid-April, 1996 and is clinically in complete remission.

She has been almost asymptomatic with only minor stiffness in her limbs; this would relate to previous bone involvement which now would appear to be in remission. On examination, I could not feel her liver and she did not have any areas of tenderness.

She appears to have had a significant response to the hyaluronic/ascorbate and it is persisting. The last time she

had chemotherapy was the latter part of October. One can conclude the chemotherapy was impacting somewhat (although it had produced marginal responses by itself in the past) but, it was the subsequent event of the administration of the higher dosages of the hyaluronan which produced an additive (cumulative) synergistic effect.

This illustrates a dramatic response to hyaluronan by itself administered only intravenously at the stated dose. Clinically, the patient appears to be doing very well and is still in remission.

There also appears to be a unique type of synergism exhibited by her treatment - the administration of cytotherapy (chemotherapy) followed two months later by doses of hyaluronic acid (sodium hyaluronate) only. (A similar type of effect was exhibited in another patient treated. I treated the patient with the dosages of hyaluronan only (at least 750 mg/dosage) followed 6-8 weeks later by low dose cytostatic 5-FU (5-Fluorouracil).

Example 5 - J.S., d.o.b. 10/09/38 (Male)

This patient developed carcinoma of the prostate in 1984 and was treated elsewhere, aggressively with a variety of hormonal treatments and cytotoxic drugs. He was first seen by me October 3rd, 1995 having failed all existing therapy and had wide spread skeletal metastases from prostate cancer. He was treated here with combination therapy initially and did have some improvement of his status. However, when seen January 2nd, 1996 he was again deteriorating.

I then initiated experimental therapy with oral HA with 1 g. every 5 days (body weight = 78 kg). His PSA continued to rise until the end of January to 399 and his pain did not decrease. February 5th we increased the dose to every three days and the patient responded dramatically with prompt relief of the bone pain. The PSA has subsequently decreased significantly and he continues on this medication. (March 27th - doing clinically very well.)

This represents a response to oral HA as the only active agent and illustrates the importance of higher dosing if initial dose is ineffective.

Example 6 - O.S., d.o.b. 25/01/31 (Male)

This patient was diagnosed with poorly differentiated adenocarcinoma - giant cell component of the lung on September 5th, 1995. He had his left lung resected. In the pathological specimen, it was noted that the tumor had extended through to the pleural lining of the lung and that all lymph nodes that were biopsied were positive for tumor. This is classified as a non-curative resection.

I first saw the patient on October 3rd, 1995. He had not been offered therapy. I treated the patient initially with chemotherapy/HA using the HA at a total dose up to 1 gram per day. The patient did not tolerate this therapy well because of the chemotherapy. Subsequently, he was changed to high doses of HA beginning December 6th, 1995 and has been carried on since then. He attends for intravenous HA - dose of 1 gram per week at home. He is stable with no demonstration of disease growth which should be apparent by now.

This patient therefore represents an aggressive carcinoma of the lung that is certainly in control using a combination of intravenous and oral HA.

Example 7 - G.W., d.o.b. 15/08/18 (Female)

This patient had poorly differentiated adenocarcinoma of the endrometrium resected June 1994. After the operative procedure she was treated intermittently with a combination of chemotherapy/HA until November 14th, 1995. She appeared to be relatively stable with her disease. Toward the end of November, she began to deteriorate. It was thus judged that she was no longer responsive to chemotherapy. Her CA-125 was elevated to 118 and her CEA was elevated to 3.5. On January 6th, 1996, I initiated experimental therapy with HA intravenously using this at a total dose of 1 gram of HA intravenously (body weight = 72 kg.). She received this for two days and then was placed on oral medication - HA 1 gram of HA every 3 days. She has continued on this until March 27th (some 27 dosages). Clinically, she had deteriorated prior to this and had a chronic cough and significant malaise and fatigue. These symptoms have now

all reversed and her cough is markedly improved. Her CA - 125 has decreased to below 30 and her CEA is down to 1.

This patient illustrates a response to intravenous and oral HA, treated subsequently only with oral HA. It again indicates the frequency of dosing required orally to maintain a response.

As many changes can be made to the embodiments without departing from the scope of the invention, it is intended that all material contained herein be interpreted as illustrative of the invention and not in a limiting sense.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. A method for the treatment of cancer comprising administering orally or systemically an effective dosage amount of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof as an active therapeutic agent, in a suitable diluent, in such amounts and over such period of time to permit the successful treatment of cancer.

2. The method of Claim 1 wherein the form of hyaluronic acid is the only active therapeutic agent in the diluent.

3. The method of Claim 1 wherein the hyaluronic acid as the active agent in a suitable diluent is administered in a dosage amount exceeding 750 mg. per 70 kg. person.

4. The method of Claim 2 wherein the hyaluronic acid as the only active agent in a suitable diluent is administered in a dosage amount exceeding 750 mg. per 70 kg. person.

5. The method of Claim 1, 2, 3, or 4 wherein the molecular weight of the form of hyaluronic acid is less than 750,000 daltons.

6. The method of Claim 1, 2, 3, 4, or 5 wherein the hyaluronic acid exceeds 1g./70 kg. person in each dosage.

7. The method of Claim 1, 2, 3, 4, 5, or 6 wherein the dosage is for oral administration.

8. The method of Claim 1, 2, 3, 4, 5, or 6 wherein the dosage is for intravenous administration.

9. The method of Claim 1, 2, 3, 4, 5, 6, 7, or 8 wherein the hyaluronic acid is a sodium hyaluronate sterile solution having the following characteristics:

pH (25 deg. C.)	5.0 to 7.0

Specific Gravity (25 deg. C.)	0.990 to 1.010
Intrinsic Viscosity	4.5 to 11.0 dL/g
Molecular Weight	178,000 to 562,000 daltons
Sodium Hyaluronate Assay	9.0 to 11.0 mg/mL
Bacterial Endotoxins (LAL) (USP 23)	NMT 0.07 EU/mg

10. The method of Claim 1, 2, 3, 4, 5, 6, 7, or 8 wherein the hyaluronic acid is a sodium hyaluronate sterile solution having the following characteristics:

pH (1% solution)	5.0 to 7.0
Intrinsic Viscosity	10.0 to 14.5 dL/g
Molecular Weight	500,000 to 800,000 daltons

11. The method of Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 wherein the form of hyaluronic acid is sodium hyaluronate.

12. The use of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and a pharmaceutically acceptable salt thereof as the active agent for treating cancer.

13. The use of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and a pharmaceutically acceptable salt thereof as the only active agent for treating cancer.

14. The use of Clam 12 or 13 wherein the hyaluronic acid as an active agent is in a suitable diluent and is in a dosage amount exceeding 750 mg. per 70 kg. person.

15. The use of Claim 12, 13, or 14 wherein the molecular weight of the form of hyaluronic acid is less than 750,000 daltons.

16. The use of Claim 13, 14, or 15 wherein the hyaluronic acid is in a suitable diluent and is in a dosage amount exceeding 1 g. per 70 kg. person.

17. The use of Claim 12 or 13 wherein the dosage is for oral administration.

18. The use of Claim 12 or 13 wherein the dosage is for intravenous administration.

19. The use of Claim 12, 13, 14, 15, 16, 17, or 18 wherein the hyaluronic acid is a sodium hyaluronate sterile solution having the following characteristics:

pH (25 deg. C.)	5.0 to 7.0
Specific Gravity (25 deg. C.)	0.990 to 1.010
Intrinsic Viscosity	4.5 to 11.0 dL/g
Molecular Weight	178,000 to 562,000 daltons
Sodium Hyaluronate Assay	9.0 to 11.0 mg/mL
Bacterial Endotoxins (LAL) (USP 23)	NMT 0.07 EU/mg

20. The use of Claim 12, 13, 14, 15, 16, 17, or 18 wherein the hyaluronic acid is a sodium hyaluronate sterile solution having the following characteristics:

pH (1% solution)	5.0 to 7.0
Intrinsic Viscosity	10.0 to 14.5 dL/g
Molecular Weight	500,000 to 800,000 daltons

21. The use of Claim 12, 13, 14, 15, 16, 17, 18, 19, or 20 wherein the form of hyaluronic acid is sodium hyaluronate.

22. The use of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and a pharmaceutically acceptable salt

thereof as the only active agent in the manufacture of a pharmaceutical composition including suitable diluents for the treatment of cancer.

23. The use of Claim 22 wherein the hyaluronic acid as the active agent is in a suitable diluent (such as saline or sterile water) and is in a dosage amount exceeding 750 mg. per 70 kg. person.

24. The use of Claim 22 or 23 wherein the molecular weight of the form of hyaluronic acid is less than 750,000 daltons.

25. The use of Claim 22, 23, or 24 wherein the hyaluronic acid is in a suitable diluent and is in a dosage amount exceeding 1 g. per 70 kg. person.

26. The use of Claim 22 wherein the dosage is for oral administration.

27. The use of Claim 22 wherein the dosage is for intravenous administration.

28. The use of Claim 22, 23, 24, 25, 26, or 27 wherein the hyaluronic acid is a sodium hyaluronate sterile solution having the following characteristics:

pH (25 deg. C.)	5.0 to 7.0
Specific Gravity (25 deg. C.)	0.990 to 1.010
Intrinsic Viscosity	4.5 to 11.0 dL/g
Molecular Weight	178,000 to 562,000 daltons
Sodium Hyaluronate Assay	9.0 to 11.0 mg/mL
Bacterial Endotoxins (LAL) (USP 23)	NMT 0.07 EU/mg

29. The use of Claim 22, 23, 24, 25, 26, or 27 wherein the hyaluronic acid is a sodium hyaluronate sterile solution having the following characteristics:

pH (1% solution)	5.0 to 7.0

Intrinsic Viscosity	10.0 to 14.5 dL/g
Molecular Weight	500,000 to 800,000 daltons

30. The use of Claim 22, 23, 24, 25, 26, 27, 28, or 29 wherein the form of hyaluronic acid is sodium hyaluronate.

31. A method for the treatment of cancer comprising administering orally or systemically at least a two-stage course of cancer treatment, one of the courses of treatment comprising administering orally or systemically effective dosage amounts of a form of hyaluronic acid selected from the group consisting of hyaluronic acid and pharmaceutically acceptable salts thereof as an active therapeutic agent in a suitable diluent over a suitable time period and, another course of therapy comprising administering orally or systemically effective dosage amounts of a chemotherapeutic agent (anti-cancer agent) over a suitable time period wherein a time period is provided between the stoppage of administration of one of the courses of administration and the beginning of the other course of administration when neither treatment is provided.

32. The method of Claim 31 wherein the course of administration comprising the form of hyaluronic acid is administered before the course of administration comprising the chemotherapeutic agent.

33. The method of Claim 31 wherein the course of administration comprising the chemotherapeutic agent is administered before the course of administration comprising the form of hyaluronic acid.

34. The method of Claim 31, 32, or 33 wherein the period of time between the end of the administration of one course of cancer treatment and the commencement of another course of cancer treatment is between about 6-9 weeks.

35. The method of Claim 31, 32, 33, or 34 wherein the hyaluronic acid as an active agent is in a suitable diluent and is in a dosage amount exceeding 750 mg. per 70 kg. person.

36. The method of Claim 31, 32, 33, 34, or 35 wherein the molecular weight of the form of hyaluronic acid is less than 750,000 daltons.

37. The method of Claim 31, 32, 33, 34, 35, or 36 wherein the hyaluronic acid is in a suitable diluent and is in a dosage amount exceeding 1 g. per 70 kg. person.

38. The method of Claim 31, 32, 33, 34, 35, 36, or 37 wherein the dosage is for oral administration.

39. The method of Claim 31, 32, 33, 34, 35, 36, or 37 wherein the dosage is for intravenous administration.

40. The method of Claim 31, 32, 33, 34, 35, 36, 37, 38, or 39 wherein the hyaluronic acid is a sodium hyaluronate sterile solution having the following characteristics:

pH (25 deg. C.)	5.0 to 7.0
Specific Gravity (25 deg. C.)	0.990 to 1.010
Intrinsic Viscosity	4.5 to 11.0 dL/g
Molecular Weight	178,000 to 562,000 daltons
Sodium Hyaluronate Assay	9.0 to 11.0 mg/mL
Bacterial Endotoxins (LAL) (USP 23)	NMT 0.07 EU/mg

41. The method of Claim 31, 32, 33, 34, 35, 36, 37, 38, or 39 wherein the hyaluronic acid is a sodium hyaluronate sterile solution having the following characteristics:

pH (1% solution)	5.0 to 7.0
Intrinsic Viscosity	10.0 to 14.5 dL./g
Molecular Weight	500,000 to 800,000 daltons

42. The method of Claim 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, or 41 wherein the form of hyaluronic acid is sodium hyaluronate.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 97/00283

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/715

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 010, no. 139 (C-348), 22 May 1986 & JP 61 000017 A (SEIKAGAKU KOGYO KK), 6 January 1986, see abstract ---	1-42
X	WO 94 20115 A (MILES INC ;BROWN KAREN K (US)) 15 September 1994 cited in the application * see claim 1, examples 1 & 2 * --- -/--	1-42

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of the international search	Date of mailing of the international search report
9 July 1997	25.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Isert, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 97/00283

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 30423 A (NORPHARMCO INC ;FALK RUDOLF EDGAR (CA); ASCULAI SAMUEL SIMON (CA)) 16 November 1995 cited in the application * see page 1, line 25 - page 3, line 9, page 18, line 10 - page 20, line 27; claims *	31-42
A	WO 92 01003 A (UNIV TEXAS) 23 January 1992 * see claims , and page 19 lines 9-14 *	1-42
A	US 5 464 942 A (SAKURAI KATSUKIYO ET AL) 7 November 1995 * see in particular col. 1, lines 45-60 *	1-42

Form PCT ISA 210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 97/00283

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9420115 A	15-09-94	AU 6362594 A	26-09-94
WO 9530423 A	16-11-95	CA 2122519 A	30-10-95
		AU 2402395 A	29-11-95
		EP 0760667 A	12-03-97
		HU 75868 A	28-05-97
		WO 9407505 A	14-04-94
		WO 9526193 A	05-10-95
		WO 9529683 A	09-11-95
		WO 9606622 A	07-03-96
		US 5614506 A	25-03-97
WO 9201003 A	23-01-92	US 5262403 A	16-11-93
		AU 8306791 A	04-02-92
US 5464942 A	07-11-95	JP 4082836 A	16-03-92
		JP 4080201 A	13-03-92
		JP 4080202 A	13-03-92
		AT 148713 T	15-02-97
		AU 647814 B	31-03-94
		AU 8226691 A	18-02-92
		CA 2067211 A	25-01-92
		DE 69124590 D	20-03-97
		DE 69124590 T	12-06-97
		EP 0493622 A	08-07-92
		WO 9201720 A	06-02-92